cc:
Archival NDA 20-986
HFD-510/Div. Files
HFD-510/J.Rhee
HFD-510/SMoore, RSteigerwalt, GTroendle
HFD-870/HAhn
HFD-713/TSahlroot
DISTRICT OFFICE

Drafted by: emg/September 28, 1998
filename: 20986AC2.nda

GENERAL CORRESPONDENCE (GC)

Food and Drug Administration
Rockville MD 20857

SEP 22 1998

NDA 20-986

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

Dear Dr. Reit:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: TRADEMARK (insulin aspart) Injection

Therapeutic Classification: Standard (S)

Date of Application: September 15, 1998

Date of Receipt: September 18, 1998

Our Reference Number: NDA 20-986

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 17, 1998, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 18, 1999.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Sincerely yours,

/S/ 9.21.98

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-986
HFD-510/Div. Files
HFD-510/J.Rhee
HFD-510/SMoore, RSteigerwalt, GTroendle
HFD-870/HAhn
HFD-713/TSahlroot
DISTRICT OFFICE

Drafted by: emg/September 21, 1998
filename: 20986AC.NDA

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

Novo Nordisk

NDA AMENDMENT
Clinical Data

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

August 10, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 1 1 1999
HFD-510

RE: **NDA 20-986** **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the fax dated August 3, 1999 from Dr Saul Malozowski containing clinical requests from Dr. Koller.

At this time we are submitting an amendment, in duplicate, containing our responses to clinical requests #1, #2, #3 and #4 of 6. We will submit the responses to requests #5 and #6 within one week.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mary Ellen Elliott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

NDA AMENDMENT
Human Pharmacokinetics and Bioavailability-Phase IV Commitment

Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

August 5, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the July 20, 1999 fax we received from Dr. Hae-Young Ahn, which contained a request that we provide a commitment to perform Phase IV studies to determine the impact on the PK/PD of insulin aspart in certain special populations.

We are providing our commitment to perform the following Phase IV studies:

1. PK/PD in renally and hepatically impaired patients
2. PK/PD in obese vs. thin patients

We expect to submit protocols for these studies by March 31, 2000.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

M A McElligott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

NDA AMENDMENT
Safety Update

August 5, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk
Pharmaceutica
Suite 200
100 Overlook C
Princeton, NJ 0
Tel. 609-987-58
Fax 609-921-80

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Further reference is made to a telephone conversation between Julie Rhee and Robert Fischer on August 3, 1999. In that conversation, Ms. Rhee requested that Novo Nordisk submit a Pre-Approval Safety Update for Insulin aspart.

At this time, we are submitting the requested Pre-Approval Safety Update. If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

M A McElligott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

ORIG AMENDMENT
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NDA AMENDMENT
Chemistry

Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

July 21, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 22 1999
HFD-510

RE: **NDA 20-986** **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to a telephone conversation between Dr. Berlin and Robert Fischer on July 21, 1999.

During the telephone call, Dr. Berlin was informed that Novo Nordisk has obtained the two remaining letters of authorization for cartridges and vials.

At this time we are submitting an amendment containing the two letters of authorization.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Karen A Hopkins per

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

cc: Field Office, North Brunswick Resident Post

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Novo Nordisk

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

NDA AMENDMENT
Chemistry

July 13, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

ORIG AMENDMENT
N-000 BC

RE: **NDA 20-986** **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to a telephone conversation between Dr. Berlin and Robert Fischer on June 17, 1999.

During the telephone call, Dr. Berlin was informed that Novo Nordisk was gathering the additional information he had requested in order to complete his review of the NDA. It was agreed that we would submit this information in one amendment.

At this time we are submitting an amendment containing the requested information.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reiv, Ph.D.
Vice President, Regulatory Affairs

Enclosure

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIG AMENDMENT
BC

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

NDA AMENDMENT
Chemistry

June 21, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to a telephone conversation between Dr. Berlin and Robert Fischer on June 15, 1999.

During the telephone call,, Dr. Berlin was informed that Novo Nordisk had additional bioassay data which we would like to be considered before a final decision is reached regarding specifications for the product.

At this time we are submitting a report entitled "HPLC-Assay and Biological Activity of Insulin Aspart" We request that after FDA review of this report, a teleconference be scheduled to discuss this issue.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mk McElwee for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cf
Enclosure

ORIGINAL

BM

ORIG AMENDMENT

NDA AMENDMENT
Clinical Data

June 16, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14)**
(recombinant DNA origin)

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Further reference is made to our amendment of June 3, 1999. At that time we submitted a revised Excel spreadsheet of data from studies ANA/DCD/036/USA and ANA/DCD/036/USA Extension following comments to the original submission by Dr. Koller.

At this time, we are submitting a diskette containing Excel spreadsheets of data from studies ANA/DCD/035/EU and ANA/DCD/037/USA and spreadsheets containing information on hypoglycemic events for the three phase III trials.

The diskette contains the WinZiped folder "Extracted Data & Hypoglycaemic Episodes", containing the following files:

Extracted Data 035.xls	Hypoglycaemic Episodes 035.xls
Extracted Data 037.xls	Hypoglycaemic Episodes 036.xls
	Hypoglycaemic Episodes 037.xls

We are providing an additional copy of the diskettes for ease of review. If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ N.A.I. ☐ M
CSO INITIALS

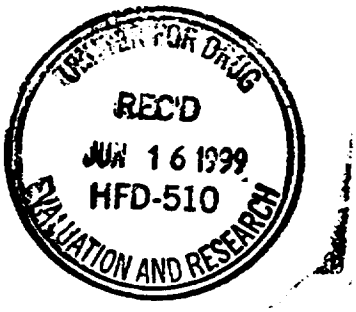
Enclosure

NDA SUPP AMEND
BC

NDA AMENDMENT
Chemistry

ORIGINAL

June 15, 1999



Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998.

At this time we are amending the NDA with the following stability report:

"Twelve-Month Interim Stability Report on Insulin Aspart , Vial 10 ml, 100 U/ml"

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Rein, Ph.D.
Vice President, Regulatory Affairs

Enclosure

cc: Field Office, North Brunswick Resident Post

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

ORIGINAL

ORIG AMENDMENT
BM

NDA AMENDMENT
Clinical Data

June 10, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 11 1999
HFD-510

Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14)**
(recombinant DNA origin)

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Further reference is made to a telephone conversation between Dr. Koller and Robert Fischer on May 24, 1999. In that conversation, Dr. Koller requested that we send information on individual patients regarding deviations in time of trial visit, certain outlying laboratory results and changes to basal insulin dosing.

At this time, we are submitting the requested information. If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

NDA AMENDMENT
Chemistry

June 8, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 20-986** **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to a telephone conversation between Dr. Berlin and Robert Fischer on May 25, 1999.

During the telephone call, Dr. Berlin requested the report referenced in NDA 20-986 Volume 2, page 146, entitled, "Comparison of Biological Potency Estimates for X14 Insulin Analogue Determined by ——————————— Report 1996 (Ref. No. 95-23)." This report is enclosed.

Dr Berlin also requested clearer copies of ——— presented in volumes 2 and 3 of the NDA. Photocopies of the following ——— are also submitted:

Volume	NDA Page	Reference	Report Page
2	35 and 36	⌜	26 and 27 of 31
2	42 to 49	⌞	
2	62		13 of 15
3	136		23 of 23
3	323 and 326		11 and 14 of 18
3	364	⌟	10 of 15

Volume	NDA Page	Reference	Report Page
3	384 and 385	[ ]	
3	406 and 408		

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cf
Enclosure

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

DATE

CSO INITIALS

APPEARS THIS WAY
ON ORIGINAL

NDA AMENDMENT
Labeling

May 28, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk
Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. In the cover letter of that submission it was stated that Novo Nordisk would prepare patient labeling and amend it to the NDA. We are now amending the NDA for insulin aspart with the patient labeling for the following product presentation:

Prefilled™ 3 mL syringe

As requested, the labeling is also submitted on a diskette.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

M a Mc Elligott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

NDA AMENDMENT
Labeling

ORIGINAL

ORIG AMEND
BL

May 27, 1999

Novo Nordisk

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-78
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. In the cover letter of that submission it was stated that Novo Nordisk would prepare patient labeling and amend it to the NDA. We are now amending the NDA for insulin aspart with the patient labeling for the following product presentations:

10 mL Vial
PenFill® 3 mL cartridge

Patient labeling for the Prefilled™ 3 mL syringe is in preparation and will be amended to the NDA as soon as possible.

As requested, the labeling is also submitted on a diskette.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

mark 1
/s/

NAI
/s/
6/14/99

ORIG AMENDMENT

BB

Novo Nordisk

NDA AMENDMENT
Human Pharmacokinetics and Bioavailability

May 26, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 27 1999
HFD-510

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the Information Request, cleared for faxing by Dr. Hae-Young Ahn, which was faxed to Novo Nordisk on May 4, 1999. Information was requested concerning the statistical analysis plan for Study 027 (Appendix H), Section 4, pertaining to an exploratory non-parametric analysis of the inter and intra-subject variability of tmax that was performed.

As requested, we are providing an amendment containing documentation to address the stated concerns.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Ina Mc Elligott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cf
Enclosure

Will Review
M+ copy
/S/
6/14/99

To Biopharm
/S/
6/2/99

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 8-10-99
CSO INITIALS

ORIGINAL

NDA AMENDMENT
Human Pharmacokinetics and Bioavailability

May 25, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk
Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: **NDA 20-986** **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the April 29, 1999 teleconference between FDA and Novo Nordisk regarding the validation of the ——— Assay as used to calculate insulin aspart levels. At that teleconference, Dr. Fossler asked Novo Nordisk to supply clarifying documentation to the validation report.

At this time we are providing the following documentation:

- A statement from ——— regarding their procedure for ——— samples

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cf
Enclosure

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 8-10-99
CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 26 1999
HFD-510

NDA AMENDMENT
Human Pharmacokinetics and Bioavailability

ORIGINAL

BB

May 13, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

WILL REVIEW

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 ~~Insulin aspart (Insulin X-14)~~ **(recombinant DNA origin)**

/S/ 6/14/99

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the April 29, 1999 teleconference between FDA and Novo Nordisk regarding the validation of the _____ Assay as used to calculate insulin aspart levels. At that teleconference, Dr. Fossler asked Novo Nordisk to supply clarifying documentation to the validation report.

At this time we are providing the following documentation:

- Calculation of precision of _____ nsulin aspart after correction for non linearity
- Calculation of precision and sensitivity of _____ based on GLP study 950106

A statement from _____ regarding their procedure for _____ samples will be provided as soon as it is available.

We are providing an additional desk copy of this amendment.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure
cc. Julie Rhee, desk copy

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

/S/ 8-10-99
CSO INITIALS DATE

NDA AMENDMENT
Human Pharmacokinetics and Bioavailability ORIGINAL

NDA ORIG AMENDMENT
BB

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 10 1999
HFD-510

Novo Nordisk
Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

May 7, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Will review my copy 5/9/99 /S/

RE: NDA 20-986 **Insulin aspart (Insulin X-14)**
(recombinant DNA origin)

Dear Dr Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the April 7, 1999 fax we received from Dr. Hae-Young Ahn, which contained a request that we provide QC data for each study in the NDA where insulin levels were measured.

At this time we are providing, attached in duplicate, QC data for five clinical trials. Those trials are:

ANA/DCD/022/UK
ANA/DCD/023/D
ANA/DCD/026/US
ANA/DCD/044/UK
ANA/DCD/045/UK

We are providing an additional desk copy of this amendment.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mia McElligott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

cc Julie Rhee, desk copy

/S/

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 8-10-99
CSO INITIALS DATE

/S/

ORIGINAL

Novo Nordisk

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

NDA AMENDMENT
Clinical Data

April 12, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Further reference is made to the cover letter to our March 31, 1999 amendment to the NDA. That amendment was the Phase III Clinical Trial Report: Six-Month Extension of ANA/DCD/036/USA. In that letter we stated that, as requested by Dr. Elizabeth Koller on March 17, 1999, we would submit an Excel spreadsheet of data from this study in the specified format.

At this time we are submitting a diskette containing a spreadsheet entitled, **"X-14 (Insulin aspart), Extracted Data from ANA/DCD/036/USA and ANA/DCD/036/USA Extension"**. We are providing an additional copy of the diskette for ease of review. If you have any questions regarding this amendment, please contact Robert Fischer, Manager, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 5-19-99
CSO INITIALS DATE

CENTER FOR DRUG ... REC'D ... 13 199 HFD-510

/S/

ORIGINAL

NDA AMENDMENT
Human Pharmacokinetics and Bioavailability

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

April 20, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 21 1999
HFD-510

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the April 7, 1999 fax we received from Dr. Hae-Young Ahn, which contained a request that we provide Novo Nordisk Internal Report No. — "Validation of ——— for Measurement of Insulin X14 and Human Insulin in Human Serum as Regards to Recovery, Linearity, and Precision".

At this time we are providing, attached in duplicate, the above mentioned report to be amended to NDA 20-986. The title of the final report is "Validation of ——— — for Quantitative Analysis of Insulin Aspart in Human Serum Samples: Recovery, Linearity, and Precision". As requested, we are providing an additional desk copy.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED
LETTER MEMO
/S/ 8-10-99
CSO INITIALS DATE

Enclosure

cc. Julie Rhee, desk copy

Will review
/S/ 6/14/99

ORIGINAL

AM

ORIG AMENDMENT

NDA AMENDMENT
Clinical Data

March 31, 1999

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 01 1999
HFD-510

RE: NDA 20-986 Insulin aspart (Insulin X-14) (recombinant DNA origin)

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Further reference is made our cover letter to the 120 day safety update, dated January 14, 1999, in which we stated that the trial report for the six month extension portion of clinical study ANA/DCD/036/USA would be submitted in March 1999. This report includes a meal test in 200 patients which was committed to FDA by Novo Nordisk.

We are now providing, in duplicate, the following Phase III Clinical Trial Report:

> **Addendum to ANA/DCD/036/USA**
> **A Six-Month Extension of ANA/DCD/036/USA:** "A Six-Month Multicenter, Randomized, Parallel, Open-label, Efficacy and Safety Comparison of the Human Insulin Analogue X14 (Insulin Aspart) and Regular, Human Insulin as Meal-Related Insulin in a Multiple Injection Regimen in Subjects with Type 1 Diabetes"

In addition, as requested by Dr. Elizabeth Koller on March 17, 1999, we are preparing an Excel spreadsheet of data from this study in the specified format. We will submit this data as soon as possible. If you have any questions regarding this amendment, please contact Robert Fischer. Manager, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mary Ellyott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

/S/

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☑ N.A.I. ☐ MEMO
8-10-99 DATE
/S/ CSO INITIALS

ORIGINAL

N-000C

NEW CORRESP

General Correspondence

Novo Nordisk

March 15, 1999

Julie Rhee
Project Manager, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 16 1999
HFD-510

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Ms. Rhee:

Reference is made to NDA 20-986 which was submitted on September 15, 1998 for Insulin aspart (Insulin X-14). At this time we propose the tradename NovoLog™ for this product.

I request that you submit this proposed name to the Agency's trademark committee for review to determine whether it will be acceptable for this product in the U.S. pending approval of the NDA.

Should you have any questions concerning this issue, please contact Robert Fischer, Manager of Regulatory Affairs at the above number.

Sincerely,
NOVO NORDISK PHARMACEUTICALS Inc.

Barry Reit, PhD.
Vice President, Regulatory Affairs

This is a chemistry name, /S/ 3/17/99

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

BB

ORIGINAL

NDA ORIG AMENDMEN

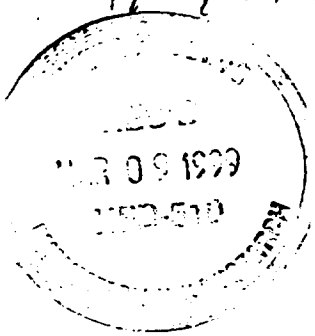
NDA AMENDMENT
Human Pharmacokinetics and Bioavailability

WILL REVIEW
M1 ONLY

March 8, 1999

/S/ 4/22/99

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk
Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the October 7, 1998 fax we received from Dr. Hae-Young Ahn, which contained a request for data on the effect of mixing insulin aspart with other long-acting insulins such as NPH and ultralente.

We are providing the requested information, in duplicate, with the following Phase I Clinical Trial Report:

> **ANA/DCD/052/UK**: "A single centre, randomised, open labelled, two-period cross-over trial in healthy subjects investigating the effect of NPH insulin on the pharmacokinetics of insulin aspart when administered as two injections or mixed prior to injection"

If you have any questions regarding this amendment, please contact Robert Fischer, Manager, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

noted /S/ 4/27/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Novo Nordisk Pharmaceuticals Inc.	03/08/99
TELEPHONE NO *(Include Area Code)* (609) 987-5800	FACSIMILE (FAX) Number *(Include Area Code)* (609) 987-3916

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-986

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Insulin Aspart

PROPRIETARY NAME *(trade name)* IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
28 -L-Aspartic Acid-Insulin (human)

CODE NAME *(If any)* Insulin X-14

DOSAGE FORM: Parenteral

STRENGTHS: 100 Units/ml

ROUTE OF ADMINISTRATION: Subcutaneous

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Diabetes Mellitus

APPLICATION INFORMATION

APPLICATION TYPE (check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)

☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached pages for manufacturing information. Company contact person is Robert Fischer, Manager Regulatory Affairs. Telephone No.: 609-987-5891, Fax No. 609-987-3916. Sites will be ready for PAI on January 2, 1999.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

IND —— NDA's 19-938
DMF Nos. ——

ORIGINAL

NDA AMENDMENT
Human Pharmacokinetics and Bioavailability

ORIG AMENDMENT

3B

Novo Nordisk

/S/ 3/11/99

February 26, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 0 1 1999
HFD-510

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

NOTED, WILL REVIEW MY COPY. /S/ 4/5/99

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the February 3, 1999 fax we received from Dr. Hae-Young Ahn, which contained a request for information regarding calculation of insulin aspart levels in study ANA/DCD/022/UK.

We are providing, attached, the information requested by the Biopharm reviewer to be amended to the above referenced NDA.

If you have any questions regarding this amendment, please contact Robert Fischer, Manager, Regulatory Affairs, at (609) 987-5891.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 4-19-99
CSO INITIALS DATE

Biopharm review pending

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

Info for Biopharm
/S/ 3/12/99

ORIGINAL

NDA AMENDMENT

ORIG AMENDMENT

February 19, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. In the cover letter to that submission it was stated that Novo Nordisk would provide stability data on three manufacturing scale batches of drug substance as it becomes available.

We are now amending the NDA with three-month stability for three launch scale batches of drug substance. Also enclosed is a diskette containing the stability data in SAS format. Each data set has been stored on the diskette in the following structure:

- Insulin Aspart drug substance (launch scale)

[redacted]

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

We are also submitting at this time, Certificates of Analysis for three launch scale batches of drug product in each of the following product presentations:

Insulin Aspart Penfill® —100 U/ml
Insulin Aspart Penfill® 3 ml, 100 U/ml
Insulin Aspart vial 10 ml, 100 U/ml

Finally, we are submitting an amendment to our Environmental Assessment. Please replace our previous Environmental Assessment, Volume 9, Section 3.5, page 118 of NDA 20-986 with the EA enclosed. The enclosed version reflects the language requested from Dr. William Berlin during his telephone conversation with Robert Fischer, and includes the statement from 21 CFR, 25.15 stating that to the best of our knowledge, no extraordinary circumstances exist which would nullify a categorical exclusion for submitting an Environmental Assessment.

If you have any questions regarding this amendment, please contact Robert Fischer, Manager, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

M H McElligott for Barry Reit.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure
BR/ROFI/paka

H:\x14nda\amendments\ — cmc amendment

**APPEARS THIS WAY
ON ORIGINAL**

NDA AMENDMENT
Chemistry Manufacturing and Controls

ORIG AMENDMENT
BI

January 29, 1999

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the January 14, 1999 fax we received from Dr. Cooney, FDA Microbiology Reviewer, which contained Microbiology comments to the submission.

As requested, we are providing an amendment containing documentation to address the stated concerns. We are also providing an additional desk copy of the amendment as requested.

If you have any questions regarding this amendment, please contact Robert Fischer, Manager, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Karen A Hopkins for

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: Desk copy
Enclosure

APPEARS THIS WAY
ON ORIGINAL

BR/ROFI/pk

NDA AMENDMENT

ORIGINAL

ORIG AMENDMENT

BC

January 21, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. In the cover letter of that submission it was stated that Novo Nordisk would change the closure for the product to one which contained ——— ——— . Novo Nordisk committed to amending the Insulin aspart NDA with new information on the container closure when it became available. We are now amending the NDA for insulin aspart with the following two reports concerning the new closure:

- Comparison of the stability of three batches of Insulin Aspart, PenFill 3 ml, 100 U/ml closed with ——— and one batch of Insulin Aspart, PenFIll, 3 ml, 100 U/ml closed with ——— and
- Compatibility testing of ——— and Insulin Aspart, 100 U/ml.

If you have any questions regarding this amendment, please contact Robert Fischer, Manager, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Enclosure
BR/ROFI/paka
H:\rofi\x14\amend\12199 closure amendment

ORIGINAL

ORIG AMENDMENT
SU

NDA AMENDMENT
120 DAY SAFETY UPDATE

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

January 14, 1999

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

JAN 1 [illegible] 1999

RE: NDA 20-986 **Insulin aspart (~~Insulin~~ X-14)**
(recombinant DNA origin)

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14). At this time we are amending NDA 20-986 to provide the referenced safety update.

This safety update includes accumulated safety information on all trials completed before August 5, 1998. For ongoing trials, information has been included on adverse event (AE) withdrawals and serious adverse events (SAEs) up to the cutoff date of August 5, 1998.

Case report forms for patients who discontinued due to adverse events are included for studies ANA/DCD/050/EU, ———— ANA/DCD/036/USA (extension) and ———— Please note that for study ANA/DCD/050/EU (the ongoing extension trial of study ANA/DCD/035/EU) the complete case report forms are not yet available but will be included in the final report for that study.

The information presented in the safety update is consistent with the draft package insert submitted with the NDA. Therefore, product labeling is not updated at this time.

In the cover letter to the NDA, we stated that the completed trial report for the ANA/DCD/036 extension study would be submitted with this update. Due to some delays in database transfer, the target date for the trial report is March 1999

at which time it will be submitted. Please note that full safety data as well as antibody data for this study are included in the safety update.

If you have any questions regarding this submission, please contact Robert Fischer, Manager, Regulatory Affairs at (609) 987-5891 or by E-mail at ROFI@Novo.dk.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mary Ann McElligott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

attachment

APPEARS THIS WAY
ON ORIGINAL

NDA AMENDMENT

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 4-19-99
CSO INITIALS DATE

ORIGINAL

ORIG AMENDMENT

November 16, 1998

Novo Nordisk
Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

NOV 17 1998

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14). Further reference is made to a telephone call from Julie Rhee, FDA, which was received by Robert Fischer on October 19, 1998. At that time, it was requested that Novo Nordisk submit data sets for the adequate and well controlled trials.

At this time, we are submitting data sets for the following studies:

ANA/DCD/035/EU
ANA/DCD/036/USA
ANA/DCD/037/USA

A document describing the procedure for importing the SAS data sets and statistical SAS programs is attached.

Please note that upon further review, we have discovered that for the 036 trial, in Selected End of Text Listing 0 the center ID numbers and addresses are correct, however, the investigator names and addresses are not aligned properly. Therefore, should you need to link the database center code, investigator name and address, we are providing, for the 036 trial, the raw data listing "subject information" which lists, for each site, the database center code, center ID and center address. Also attached is a listing of the principal investigators, site addresses and site numbers (center ID).

/S/

As requested by Julie Rhee, an additional copy of all information has been included.

If you have any questions regarding this submission, please contact Robert Fischer, Manager, Regulatory Affairs.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: Julie Rhee, Project Manager

attachment

APPEARS THIS WAY
ON ORIGINAL

NDA AMENDMENT

ORIG AMENDMENT

October 20, 1998

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

OCT 21 1998

EVALUATION AND RESEARCH

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986

Insulin aspart (Insulin X-14)
(recombinant DNA origin)

Dear Dr. Sobel:

Reference is made to NDA 20-986 which was submitted on September 16, 1998 for Insulin aspart (Insulin X-14). Further reference is made to our amendment of October 9, 1998 to NDA 20-986.

At this time, we are submitting data sets for the following studies: ANA/DCD/023/DK, ANA/DCD/027/D on a compact disc and ANA/DCD/026/US on two diskettes. Brief descriptions of the Microsoft Excel files are attached.

As requested in the fax communication dated 10/7/98 from Dr. Hae-Young Ahn, the data tape submissions include raw insulin concentrations for all pharmacokinetic studies. When performing analyses on the raw data, it should be noted that the insulin aspart numbers are raw read outs from the ——————————. assay. The standard curve for insulin aspart is different from human insulin, as validated in study No. 950106 from Novo Nordisk, Pharmaceuticals Development, Immunochemistry, which is submitted in the insulin aspart NDA vol. 31 page 146. To perform analyses on the raw assay data, the insulin aspart values therefore must be transformed to insulin aspart concentrations using the formula:

Aspart_corrected = (——*Lab_Aspart)/(——-Lab_Aspart)

where "Lab_aspart" is the raw number as reported from the laboratory.

As requested by Julie Rhee, an additional copy of all information has been included. If you have any questions regarding this submission, please contact Robert Fischer, Manager, Regulatory Affairs.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reitz, Ph.D.
Vice President, Regulatory Affairs

attachment

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

ORIGINAL

NDA AMENDMENT

ORIG AMENDMENT

October 8, 1998

Novo Nordisk
Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 which was submitted on September 16, 1998 for Insulin aspart (Insulin X-14). Further reference is made a fax communication from Julie Rhee, FDA, which was received by Robert Fischer on June 10, 1998. This communication contained Biopharm review comments to Novo Nordisk's May 14, 1998 submission outlining the proposed format for the NDA. The comments stated that:

1. Novo Nordisk should submit study synopses in Word version 7.x and PK and PD data in either Excel format (preferred) or ASCII format for each study considered pivotal to the proposed labeling, submitted to Section VI (Human Bioavailability and Pharmacokinetics). For each study, both raw concentration vs. time data and calculated parameters should be provided, if possible.

2. A copy of the proposed labeling (annotated) should be submitted in Word version 7.x.

Novo Nordisk committed to submitting the requested information within 30 days of the submission of the NDA.

At this time, we are submitting study synopses in Word format for the following studies:

1 *Clinical Pharmacology Trials - Healthy Subjects*

ANA/DCD/022/UK
ANA/DCD/044/UK
ANA/DCD/045/UK
ANA/DCD/023/D
ANA/DCD/026/USA
ANA/DCD/027/D
ANA/DCD/039/UK

2 *Clinical Pharmacology Trials - Diabetic Subjects*

ANA/DCD/024/UK

ANA/DCD/043/DK

ANA/DCD/030/DK/N

3 ——— *Clinical Pharmacology Trials*

Also, please find copies of the annotated labeling in Word format.

In addition, we are submitting data sets for the following studies ANA/DCD/022/UK, ANA/DCD/024/UK, ANA/DCD/030/DK/N, ANA/DCD/039/UK and ANA/DCD/043/DK. A brief description of the Microsoft Excel files is attached. Data sets for three additional trials, ANA/DCD/023/DK, ANA/DCD/026/US and ANA/DCD/027/D will follow in a separate submission.

As requested in the fax communication dated 10/7/98 from Dr. Hae-Young Ahn, the data tape submissions will include raw insulin concentrations for all pharmacokinetic studies. When performing analyses on the raw data, it should be noted that the insulin aspart numbers are raw read outs from the ——— assay. The standard curve for insulin aspart is different from human insulin, as validated in study No. 950106 from Novo Nordisk, Pharmaceuticals Development, Immunochemistry, which is submitted in the insulin aspart NDA vol. 31 page 146. To perform analyses on the raw assay data, the insulin aspart values therefore must be transformed to insulin aspart concentrations using the formula:

Aspart_corrected = (——— *Lab_Aspart)/ ———-Lab_Aspart)

where "Lab_aspart" is the raw number as reported from the laboratory.

As requested by Julie Rhee, an additional copy of all information has been included.

If you have any questions regarding this submission, please contact Robert Fischer, Manager, Regulatory Affairs.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

MA McElligott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

attachment

APPEARS THIS WAY
ON ORIGINAL

September 15, 1998

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to IND —— which was filed on June 29, 1995 for Insulin aspart (Insulin X-14) for the treatment of diabetes mellitus. We are herewith submitting an original NDA for this product. Insulin aspart is a new molecular entity and is an injectable rapid acting human insulin analog. Insulin aspart differs from regular human insulin by its rapid onset and shorter duration of action. Because of the fast onset of action, the injection of insulin aspart should be made immediately before a meal.

Novo Nordisk is filing for approval of this product in the following packaging presentations:

10 ml vial

PenFill® 3 ml cartridge

Prefilled® 3 ml syringe

Please note that, as reflected in the labeling, the intent of Novo Nordisk is to market only the 10 ml vial, PenFill® 3 ml cartridge and Prefilled® 3 ml syringe at the present time. PenFill® 3 ml cartridges are designed to be used in the NovoPen 3 insulin pen which was approved by FDA in NDA 19-938 S/021 for Novolin® R. Should Novo Nordisk decide to market the other presentations, labeling will be submitted to FDA for review. Please note, also, that, in the NDA, the term "Novolet" is used to describe the Prefilled syringe. Novolet™ is the approved name for the Prefilled syringe in Europe.

The NDA contains an annotated physician's package insert and draft carton, vial and cartridge labeling referring to the tradename ———— which has been applied for but has not been approved by FDA. When a tradename has been approved, updated draft labeling will be amended to the NDA. A patient insert will also be prepared and amended to the NDA.

This application is formatted according to 21CFR §314.50 and follows the "Guideline on Formatting, Assembling and Submitting New Drug and Antibiotic Applications", the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" and the "Guidance for the Submission of Chemistry, Manufacturing and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In-Vivo Use". The initial User Fee due for this submission has been paid (Form 3397 is provided). A debarment statement and patent certification are included.

The following agreements for this NDA have been made between the Food and Drug Administration (FDA) Division of Metabolism and Endocrine Drugs and Novo Nordisk regarding the filing of this application:

On April 7, 1997 statistical review comments were received from FDA to the phase III protocols. Novo Nordisk responded to these comments on June 30, 1997 and provided a draft statistical analysis plan for the phase III studies. FDA sent further comments to the draft statistical analysis plan on August 13, 1997. A telephone conference was held on September 23, 1997 to discuss the analysis plan. The following points were agreed upon:

- In the final statistical analysis plan the primary endpoint in phase III, HbA_{1c}, would be changed to a criteria of proving non-inferiority of insulin aspart to human insulin, while taking the comparative hypoglycemia rates into account.

- Novo Nordisk agreed to include a meal-test in approximately 200 patients in the ongoing trial ANA/DCD/036/US which would explore the impact of insulin antibodies on postprandial plasma glucose control for insulin aspart and regular human insulin. The final report will be submitted with the 120 day safety update.

In a Pre-NDA CMC Meeting held on April 15, 1998 between representatives of the Division of Metabolism of Endocrine Drugs and the Office of New Drug Chemistry (FDA) and Novo Nordisk it was agreed that:

On June 10, 1998 a fax communication from Julie Rhee, FDA, was received by Robert Fischer. This communication contained Biopharm review comments to Novo Nordisk's May 14, 1998 submission outlining the proposed format for the NDA. The comments stated that:

1. Novo Nordisk should submit study synopses in Word version 7.x and PK and PD data in either Excel format (preferred) or ASCII format for each study considered pivotal to the proposed labeling, submitted to Section VI (Human Bioavailability and Pharmacokinetics). For each study, both raw concentration vs. time data and calculated parameters should be provided, if possible.

2. A copy of the proposed labeling (annotated) should be submitted in Word version 7.x.

Novo Nordisk will submit the requested information within 30 days of the submission of the NDA.

As agreed in a telephone conversation between Robert Fischer and Dr. William Berlin, FDA, on August 17, 1998, Novo Nordisk will submit analytical test methods and method validation reports for the drug substance and drug product in Section IV (Samples, Methods Validation and Labeling) only.

As agreed in a telephone conversation between Robert Fischer and Julie Rhee, FDA, on August 31, 1998, a desk copy of the Sterilization Validation documentation is included in the application to be forwarded to the Microbiology reviewer. This copy is bound in a white Microbiology binder. The original NDA pagination has been retained in these volumes.

The following points refer to the format of this NDA:

Certain preclinical study reports performed with old drug substance material which have been repeated with the current material have been excluded from Item 5 of the NDA. All preclinical study reports have been submitted to the IND. A list of all study reports not included in the NDA are included in the Nonclinical Pharmacology and Toxicology section of the NDA.

Patient data listings (PDL) for the adequate and well controlled clinical trials are included in Item 11 only. This data is tabulated for each individual study by patient and contains the same data as called for in 21 CFR 314.50 (f) (1). Patient data listings for all other studies are submitted as attachments to the clinical study reports.

Case Report Forms (CRF) for patients who died or withdrew from clinical trials due to an adverse event from the adequate and well controlled clinical trials are included in Item 12 only. Case Report Forms for all other studies are submitted as attachments to the clinical study reports.

The 120 day Safety Update will be a re-analysis of all safety data. In addition to the Integrated Summary of Safety, the 120 day safety update will contain safety information from the trials ANA/DCD/050, ANA/DCD/036 ext., [redacted] and cover the period from the clinical cut-off-date of December 5, 1997 to a cut-off-date of August 5, 1998. As study [redacted] will be ongoing at the cutoff date, the 120 day safety update will include only serious adverse events and demographic information for that study.

Upon request, Novo Nordisk will submit the following electronically:

- Clinical trial reports and the corresponding data set for the adequate and well controlled trials.

- Integrated clinical summaries and the corresponding data set.

If you have any questions regarding this submission, please contact Robert Fischer, Manager, Regulatory Affairs.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Maine Ellegott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

attachment
cc. Field Copy with certification submitted to
Food and Drug Administration
10 Waterview Blvd.
Parsippany, N.J. 07054

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Novo Nordisk Pharmaceuticals Inc.	09/15/98
TELEPHONE NO. *(Include Area Code)* (609) 987-5800	**FACSIMILE (FAX) Number** *(Include Area Code)* (609) 987-3916
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 100 Overlook Center, Suite 200 Princeton, NJ 08540-7810	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

OCT 5 1998

EVALUATION

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Insulin Aspart	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
28 -L-Asparbc Acid-Insulin (human)	Insulin X-14

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Parenteral	100 Units/ml	Subcutaneous

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Diabetes Mellitus

APPLICATION INFORMATION

APPLICATION TYPE (check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application

TYPE OF SUBMISSION (check one)

☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Original New Drug Application

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 266 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached pages for manufacturing information. Company contact person is Robert Fischer, Manager Regulatory Affairs. Telephone No.: 609-987-5891, Fax No.: 609-987-3916 .Sites will be ready for PAI on January 2, 1999.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

IND —— NDA's 19-938

DMF Nos. ——

AC meeting was not held.

There are no FR notices.

This product is to be marketed as Rx.

This product is not a DESI product.

Advertising material is not available.

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II (HFD-870)

Memorandum

To:	Julie Rhee, CSO NDA 20-986	/S/ 10/7/98
From:	Michael J. Fossler	
Through:	Hae-Young Ahn, Team Leader	/S/ 10/7/98
Date:	6 October 1998	
Re:	45 Day Filing Memo for NDA 20-986 (Insulin Aspart)	

Novo Nordisk has submitted NDA 20-986 for Insulin Aspart, a fast-acting analog of human insulin. By substituting aspartic acid for proline at position 28 in the B-chain, there is reduced insulin hexamer formation, which results in faster absorption. Insulin aspart will be marketed in 10 ml vials and 3 ml syringes, as well as 3 ml cartridges for the NovoPen® automatic injection device. Insulin aspart should be dosed immediately before meals.

A total of 12 clinical pharmacology trials were performed for insulin aspart. Trials were performed in normal volunteers, Type 1 diabetic patients (adult and pediatric), and Type 2 patients. The attached tables summarize the results. The data show that insulin aspart is absorbed faster than human insulin, as shown by its higher Cmax and shorter tmax. The extent of absorption of insulin aspart is similar to human insulin. Validation data for the two assays used in the trials were included. Notably, a mixing study to determine whether the fast absorption of insulin aspart is preserved when mixed with NPH or Ultralente was not performed. A similar product (insulin lispro) showed a great decrease in the rate of absorption when mixed with NPH. Ultralente had no effect.

The firm has "corrected" the insulin concentration data from normal volunteers for baseline endogenous insulin by using c-peptide levels. The uncorrected data will be requested by the reviewer.

Recommendation

NDA 20-986 is filable from a clinical pharmacology/biopharmaceutics perspective. The comments below should be sent to the firm.

Comments to be sent to firm:

1) When submitting the raw insulin concentration vs. time data for all studies, the data uncorrected for c-peptide levels should be submitted in addition to the corrected data.
2) Please provide any data on the effect of mixing insulin aspart with other long-acting insulins such as NPH and ultralente.

CC: HFD-870(Ahn, Chen, M.) Central Document Room (Barbara Murphy)

Trial Tabulation A.1 Clinical Pharmacology Trials - Healthy Subjects

Trial ID (ANA/DCD/) Investigator	Trial Type and Design	Treatment/Dose Duration of Treatment	Treated/ dose (total)	Age Range, years (mean) Sex (M/F) Race (B/W/O) Subjects	Conclusions
022/UK 31/1/95, 12/7/95	*Pharmacokinetic/ pharmacodynamic* Randomized, double-blind, 2-period crossover	*IAsp*: 0.1 U/kg, s.c. *HI*: 0.1 U/kg, s.c. 2 single doses; minimum 1-week washout between doses	24 25 (25)	19-50 (31) 25 M (100%) 25 W (100%) 25 fasting healthy subjects	- IAsp was absorbed faster and returned faster to baseline than HI did as assessed by an earlier $t_{max(glu)}$ and a shorter MRT. - AUC_{Ins} and $C_{max(Ins)}$ were significantly higher for IAsp than for HI. - $\Delta C_{min(glu)}$ was significantly larger and $t_{max(glu)}$ was significantly earlier for IAsp than for HI. There was no statistically significant difference in AUC_{glu}. - No SAEs were reported. No subject withdrew due to an AE. - 20 subjects had a total of 45 non-serious AEs: 26 occurred after treatment with IAsp and 19 after treatment with HI.
023/D Dr. T. Heise 3/2/95, 20/4/95	*Euglycaemic clamp* Randomized, double-blind, 2-period crossover	*IAsp*: 0.2 U/kg, s.c. *HI*: 0.2 U/kg, s.c. 2 single doses; 1- to 2-week washout between doses	24 24 (24)	18-34 (26) 24 M (100%) 24 W (100%) 24 healthy subjects	- IAsp was absorbed faster and the onset of action was faster as demonstrated by an earlier and higher C_{max} and an earlier $tGIR_{max}$. - The duration of action of IAsp was shorter than that of HI as assessed by a earlier $t_{AUC\%}$. - AUC_{GIR} was statistically significantly lower for IAsp than for HI. - AUC_{Ins} was statistically significantly higher for IAsp than for HI, whereas t_{max} and MRT were statistically significantly earlier/shorter for IAsp. - No SAEs were reported. No subject withdrew due to an AE. - 2 mild AEs were reported: hyperbilirubinemia and elevated GOT (ASAT) levels.

Trial Tabulation A.1 Clinical Pharmacology Trials - Healthy Subjects

Trial ID (ANA/DCD/) Investigator	Trial Type and Design	Treatment/Dose Duration of Treatment	Treated/ dose (total)	Age Range, years (mean) Sex (M/F) Race (B/W/O) Subjects	Conclusions
026/USA 16/3/96, 23/7/96	*Euglycaemic clamp* Randomized, double-blind, 6-period crossover	*IAsp*: 0.2 U/kg, s.c. *HI*: 0.2 U/kg, s.c. 6 single doses; minimum 1-week washout between doses	20 20 (20)	19-40 (31) 20 M (100%) 2 B; 14 W; 4 O (10%/70%/20%) 20 healthy subjects	- The onset of the glucose lowering action of IAsp did not differ between injection sites as assessed by similar $tGIR_{max}$. However, the duration of the glucose lowering action was shorter for the abdominal injections than for the deltoid or thigh injections, as assessed by $t_{AUC\%}$. The total amount of glucose infused was 10-14% lower for the abdomen than for the other sites. GIR and insulin parameters for IAsp in deltoid and thigh injections were clinically and statistically similar. - The pharmacodynamic data from this euglycaemic clamp study showed a more rapid and shorter-acting glucose lowering action of IAsp compared with HI as assessed by t_{max} and $t_{AUC\%}$. The maximal glucose infusion rate (GIR_{max}) was higher for IAsp than for HI for each of the three injection sites. IAsp was absorbed more rapidly, reached a higher maximal concentration and had a lower MRT than HI did. - No SAEs were reported. No subject withdrew due to an AE. - 1 mild AE was reported during treatment with HI.
027/D 6/11/95, 26/2/96	*Euglycaemic clamp/ Intra-/inter-subject variations* Randomized, double-blind, parallel-group	*IAsp*: 0.2 U/kg, s.c. *HI*: 0.2 U/kg, s.c. 4 single doses; 4- to 21-day washout between doses	10 10 (20)	IAsp: 22-27 (25) HI: 22-28 (25) 20 M (100%) 20 W (100%) 20 healthy subjects	- IAsp displayed a lower intra-subject variability in the time to peak concentration ($t_{max(free)}$) and time to peak effect ($tGIR_{max}$) compared to HI. - There were no other major differences in the intra- and inter-subject variability in pharmacokinetic or pharmacodynamic parameters. - IAsp exhibited a more rapid time action profile, a shorter duration of action and a more intense maximal effect compared to HI. - No SAEs were reported. One subject in the IAsp group withdrew due to thrombophlebitis (moderate; trial product relation: possible). - 6 AEs were reported: 3 in each treatment group.

Trial Tabulation A.1 Clinical Pharmacology Trials - Healthy Subjects

Trial ID (ANA/DCD/) Investigator	Trial Type and Design	Treatment/Dose Duration of Treatment	Treated/ dose (total)	Age Range, years (mean) Sex (M/F) Race (B/W/O) Subjects	Conclusions
039/UK 18/7/97, 19/11/97	*Ventricular repolarization* Randomized, double-blind, 2-period crossover	*IAsp*: 1.5 mU/kg/min, i.v. *HI*: 1.5 mU/kg/min, i.v. 2 single doses given over 120 min; 28- to 56-day washout between doses	17 17 (17)	18-39 (28) 17 M (100%) 17 W (100%) 17 healthy subjects	- QTc did not differ between treatments as assessed by ANCOVA analysis and supported by equivalence in QT dispersion. - For the primary endpoint, QTc, the upper C.I. limit was below —. - Equivalence was obtained with regard to electrolyte, noradrenaline and glucagon plasma concentrations. Equivalence was not obtained for plasma adrenaline, but there was no statistically significant difference between the treatments. - Clearance of the two insulins was similar. - No SAEs were reported. No subject withdrew due to an AE. - Two subjects had AEs (headache and migraine) which were judged as related to IAsp treatment.
044/UK 26/9/96, 8/2/97	*Bioequivalence/ pharmacokinetic/sex* Randomized, double-blind, 2-period crossover	*IAsp*: 0.06 U/kg, s.c., Old Method 0.06 U/kg, s.c. New Method 2 single doses; 4- to 10-day washout between doses	24 25 (25)	Total: 20-47 (39) Men: 20-47 (33) Women: 20-32 (26) 13 M (52%); 12 F (48%) 25 W (100%) 25 fasting healthy subjects	- Based on the analysis of $AUC_{(0-180)}$, bioequivalence between IAsp New Method and IAsp Old Method was established when the 2 subjects who were likely not to have received the full dose of IAsp New Method were excluded. - Bioequivalence between IAsp Old and New Method was supported by the analysis of t_{max} and $AOC_{(0-180)}$, C_{max} and t_{max}. - There were no statistically significant differences between men and women for $AUC_{(0-180)}$. - No SAEs were reported. One subject withdrew due to AEs (loss of consciousness and tremor) after administration of IAsp New Method. The event was considered to be due to hypoglycaemia or a vasovagal attack. - The incidence, severity and type of AEs for IAsp Old Method and IAsp New Method were similar, and the majority of AEs were related to hypoglycaemia.

Trial Tabulation A.1 Clinical Pharmacology Trials - Healthy Subjects

Trial ID (ANA/DCD/) Investigator	Trial Type and Design	Treatment/Dose Duration of Treatment	Treated/ dose (total)	Age Range, years (mean) Sex (M/F) Race (B/W/O) Subjects	Conclusions
045/UK [redacted] 18/9/97, 12/12/96	*Pharmacokinetic* Randomized, open-label, 2-period crossover	*IAsp*: 0.08 U/kg, s.c. *ILis*: 0.08 U/kg, s.c. 2 single doses; 4- to 10-day washout between doses	25 23 (27)	19-50 (28) 27 M (100%) 27 W (100%) 27 fasting healthy subjects	- A statistically significant difference was demonstrated in AUC[illegible] for IAsp being 90% of that for ILis. Based on the analysis of AUC[illegible], equivalence between IAsp and ILis was established. - For C[illegible] the 90% confidence interval (77% to 95%) was outside the specified [redacted] interval, and the results showed that ILis reached a significantly higher maximum insulin level (C[illegible]) than IAsp did by approximately 14%. - Equivalence was demonstrated for C[illegible] and AOC[illegible] and for MRT[illegible]. There was no statistically significant difference in t[illegible] and no clinically relevant difference in t[illegible] was shown. - No SAEs were reported. Eight subjects were withdrawn from the trial: 7 due to hypoglycaemia or AEs related to hypoglycaemia (4 after injection of IAsp and 3 after injection of HI) and one due to vomiting. - The safety profile was similar between treatments and the majority of AEs appeared to be related to hypoglycaemia.

APPEARS THIS WAY
ON ORIGINAL

Trial Tabulation A.2 Clinical Pharmacology Trials - Diabetic Subjects

Trial ID (ANA/DCD/) Investigator	Trial Type and Design	Treatment/Dose Duration of Treatment	Treated/ dose (total)	Age Range, years (mean) Sex (M/F) Race (B/W/O) Subjects	Conclusions
Type 1 Diabetic Subjects					
024/UK 8/5/95, 5/2/96	*Therapeutic response/ pharmacokinetic* Randomized, double-blind, double-dummy, 3-period crossover, meal-test	*IAsp*: 0.15 U/kg, s.c., 0 min *HI*: 0.15 U/kg, s.c., 0 min 0.15 U/kg, s.c., -30 min 3 single doses; minimum 1-week washout between doses	24 23 23 (24)	20-50 (33) 24 M (100%) 24 W (100%) 24 Type 1 diabetic subjects	- IAsp showed improved postprandial glucose control compared to HI as assessed by a significantly lower EXC for IAsp than for HI_{0min} and HI_{-30min}. $C_{max(glu)}$ was significantly lower for IAsp than for HI_{0min} but not significantly different from HI_{-30min}. There were no statistically significant differences in $C_{min(glu)}$ or $t_{max(glu)}$ between IAsp and HI treatments. - AUC_{tot} and $C_{max(glu)}$ were significantly higher for IAsp than for both HI treatments. MRT and $t_{max(glu)}$ were significantly shorter/earlier for IAsp than for HI_{0min}. - No SAEs were reported. One subject withdrew due to AEs (cough and cold). - 20 subjects had a total of 72 AEs: 30 occurred following treatment with IAsp, 25 following treatment with HI_{0min} and 17 following treatment with HI_{-30min}. The most frequent AEs were hypoglycaemia and headaches.

Trial Tabulation A.2 Clinical Pharmacology Trials - Diabetic Subjects

Trial ID (ANA/DCD/) Investigator	Trial Type and Design	Treatment/Dose Duration of Treatment	Treated/ dose (total)	Age Range, years (mean) Sex (M/F) Race (B/W/O) Subjects	Conclusions
025/UK 7/4/95, 14/11/95	*Therapeutic response* Multi-centre, randomized, double-blind, 2-period crossover	*IAsp*: 100 U/ml, s.c., 0 min *HI*: 100 U/ml, s.c., 0 min Dosage was adjusted throughout the trial on an individual basis, according to a trial-specific dosage adjustment schedule. 4-week run-in period followed by two 4-week treatment periods	102 100 (104)	17-54 (34) 104 M (100%) 101 W (97%), 3 O (3%) 104 Type 1 diabetic subjects	- The overall metabolic control obtained with IAsp was equivalent to the control obtained with HI, as determined by serum fructosamine. - The in-patient 23-hour profiles confirmed a lower daytime BG and a higher night time BG during IAsp treatment than during HI treatment: C_{max} and C_{min} morning and afternoon were significantly lower for IAsp. C_{min} night was statistically significantly higher for IAsp. - Glucose excursion outside the range 4 - 7 mmol/l (ΔAUC) was significantly lower with IAsp than with HI. - The per-protocol analysis showed a trend towards fewer major hypoglycaemic events per patient while on IAsp during the last 2 weeks of treatment. An explorative analysis showed a statistically significantly lower number of major hypoglycaemic events per patient during the 4-week treatment period while on IAsp than while on HI. - 3 SAEs were reported during run-in and 4 during treatment: 2 with IAsp and 2 with HI, with 1 severe hypoglycaemia accompanied by convulsions in each group. - 2 subjects withdrew due to AEs: 1 during run-in and 1 due to fatigue and anorexia during IAsp treatment. - There were no statistically significant differences in the number of AEs between IAsp and HI. - The trial showed a trend towards more basal insulin being required during treatment with IAsp.
028/UK 1/2/96, 16/1/97	*Hypoglycaemic symptom threshold/ counter-regulatory hormone response* Randomized, double-blind, 2-period crossover	*IAsp*: 2 mU/kg/min, i.v. *HI*: 2 mU/kg/min, i.v. 2 single doses given until BG <2 mmol/l or symptoms of hypoglycaemia; 3- to 6-week washout between doses	16 16 (16)	18-44 (29) 10 M (62%), 6 F (38%) 16 W (100%) 16 Type 1 diabetic subjects	- IAsp elicits the same clinical hypoglycaemic counterregulatory and symptom responses as HI does. - No SAEs were reported. No subject withdrew due to an AE after dosing. - 16 subjects had a total of 11 non-serious AEs: 5 following treatment with IAsp and 6 following treatment with HI. - IAsp and HI had similar safety profiles with respect to the type and frequency of AEs.

Trial Tabulation A.2 Clinical Pharmacology Trials - Diabetic Subjects

Trial ID (ANA/DCD/) Investigator	Trial Type and Design	Treatment/Dose Duration of Treatment	Treated/ dose (total)	Age Range, years (mean) Sex (M/F) Race (B/W/O) Subjects	Conclusions
043/DK 25/8/97, 1/12/97	*Pharmacokinetic/ paediatric* Randomized, double-blind, 2-period crossover, meal-test	*IAsp*: 0.15 U/kg, s.c., 0 min *HI*: 0.15 U/kg, s.c., 0 min 2 single doses; minimum 3-day washout between doses	18 18 (18)	Total: 7-17 (12) 6-12 years: 7-12 (9) 13-17 years: 13-17 (15) 6 M (33%); 12 F (67%) 18 W (100%) 18 Type 1 diabetic subjects	- The pharmacokinetic differences between IAsp and HI in Type 1 diabetic children and adolescents were similar to those observed in adults based on insulin C_{max}, AUC_{0-3h} and t_{max}. - The postprandial glucose control tended to improve with IAsp compared to HI as assessed by a 22% lower $EXC_{0-4h(glu)}$. - No SAEs were reported. No subject withdrew due to an AE. - A total of 8 AEs were reported after dosing: 3 occurred after administration of IAsp and 5 occurred after administration of HI. All AEs were mild or moderate. One subject reported 2 AEs (mild hypoglycaemia) that were evaluated as possibly or probably related to the trial product: one after IAsp and one after HI.
Type 2 Diabetic Subjects					
030/DK/N 16/4/96, 16/1/97	*Therapeutic response/ pharmacokinetic* Randomized, double-blind, double-dummy, 3-period crossover, meal-test	*IAsp*: 0.15 U/kg, s.c., 0 min *HI*: 0.15 U/kg, s.c., 0 min 0.15 U/kg, s.c., -30 min 3 single doses; 1- to 2-week washout between doses	24 23 24 (24)	43-71 (60) 13 M (54%), 11 F (46%) W (100%) Type 2 diabetic subjects	- Analysis of the glucose endpoints demonstrated an improved postprandial glucose control when comparing IAsp with HI_{0min}, based on a statistically significantly smaller EXC and supported by a statistically significantly lower $C_{max(glu)}$. - No difference in glucose endpoints between IAsp and HI_{-30min} could be demonstrated. - Due to the trial design, the standard methods for estimating the trial product insulin could not be applied and the planned pharmacokinetic endpoints could not be analysed. - An explorative non-comparative analysis of IAsp, using a new specific assay, confirmed that IAsp was absorbed. Mean t_{max} was 75.5 (± 41.7) min. - No SAEs were reported. No subject withdrew due to an AE. - 24 subjects had a total of 18 AEs: 6 following IAsp, 5 following HI_{0min} and 7 following HI_{-30min}. The most common AEs were rhinitis and hypoglycaemia.

Trial Tabulation B.1 Summary of Pharmacokinetic Parameters - Healthy Subjects

Trial ID[a] (ANA/DCD/)	Treatment	Dose (U/kg)	Treated	N	Mean AUC (mU/l x min)			Median F(AUC)[b]	Mean C_{max} (mU/l)	Median t_{max} (min)	Mean MRT (min)	Harmonic Mean $t_{1/2}$ (min)	Mean CL (l/hr/kg)
					0-8h	0-10h	0-∞						
022/UK	IAsp	0.1	24	19	6461	-	6740	1.12	40.9	40.0	149[c]	81	-
044/UK	IAsp (old)	0.06	24	21	-	43.5[c]	-		19.9	40.0	-	110	-
	Men			11	-	39.8[c]	-		19.1	40.0	-	-	-
	Women			10	-	46.4[c]	-		20.6	40.0	-	-	-
	IAsp (new)	0.06	25	21	-	40.3[c]	-		19.0	40.0	-	127	-
	Men			11	-	42.4[c]	-		18.3	40.0	-	-	-
	Women			10	-	44.3[c]	-		19.7	40.0	-	-	-
045/UK	IAsp	0.08	25	19		63.2[c]	-		26.2	40.0	140[c]	102	-
023/UK	IAsp	0.2	24	24	-	21400	-		125.8	50.0	102[c]	-	-
026/USA	IAsp: Abdomen	0.2	20	19	-	9556	-		75.5	50.0	109[c]	-	-
	Deltoid	0.2	20	20	-	9705	-		74.3	50.0	121[c]	-	-
	Thigh	0.2	20	19	-	9142	-		62.1	40.0	136[c]	-	-
027/D	IAsp	0.2	10	39[f]	-	17300	-		106.3	50.0	178[c]	-	-
039/UK	IAsp	0.15	17	17	-	-	-		-	-	-	-	1.22

a The assay used in all the trials in healthy subjects was the _____
b Relative to human insulin (t = 0 min)
c The units are mU/l·h.
d The time interval is 0 to 8 hours.
e The time interval is 0 to 10 hours.
f N represents the total number of insulin profiles for all the subjects for the 4 dosing days.

Trial Tabulation B.2 Summary of Pharmacokinetic Parameters - Diabetic Subjects

Trial ID (ANA/DCD/)	Treatment	Dose (U/kg)	Treated	N	Mean AUC (mU/l x min)			Median F(AUC)[a]	Mean C_{max} (mU/l)	Median t_{max} (min)	Mean MRT (min)	Harmonic Mean $t_{1/2}$ (min)
					0-5h	0-6h	0-∞					
024/UK[b]	IAsp	0.15	24	22	-	11836	14338	1.01	82.1	40.0	122[e]	122
043/DK[b]	IAsp: All	0.15	18	18	339[d]	-	580[d]		147	40.0	111[f]	187[g]
	6-12 years		9	9	240[d]	-	334[d]		121	40.0	105[f]	176[g]
	13-17 years		9	9	438[d]	-	826[d]		173	40.0	116[f]	197[g]
030/DK/N[c]	IAsp	0.15	24	22	-	-	206[d]		58.6	60.0	132	76.0[h]

a Relative to human insulin (t = 0 min)
b The assay used was the
c The assay used was the
d The units are mU/l x h.
e The time interval is 0 to 6 hours.
f The time interval is 0 to 5 hours.
g Arithmetic mean
h N=21

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Trial Tabulation C.1 Drug Formulation - Healthy Subjects

Trial ID (ANA/DCD/)	Treatment, Dose	Treated/ Dose	Batch No.; Date Manufactured Formulation/manufacturing Change Batch Size	Related IND or NDA Nos.	Submission Date	Previous Agency Responses on Trial or Protocol with Date of Correspondence
022/UK	IAsp, 0.1 U/kg	24	07794; 23/11/94 Old production method			
044/UK	IAsp, 0.06 U/kg	24	C96009; 4/3/96 Old production method			
	IAsp, 0.06 U/kg	25	C96017; 20/5/96 New production method			
045/UK	IAsp, 0.08 U/kg	25	C96017; 20/5/96 New production method			
023/D	IAsp, 0.2U/kg	24	07794; 23/11/94 Old production method			
026/USA	IAsp, 0.2U/kg	20	C95001; 16/5/95 Old production method		29/6/95	8/8/95; 9/8/95; 15/9/95; 14/11/95
027/D	IAsp, 0.2U/kg	10	C95001; 16/5/95 Old production method			
039/UK	IAsp, 15 mU/kg/min	17	C96024; 26/9/96 New production method		29/6/95	19/6/96

Trial Tabulation C.2 Drug Formulation - Diabetic Subjects

Trial ID (ANA/DCD/)	Treatment, Dose	Treated/ Dose	Batch No.; Date Manufactured Formulation/manufacturing Change Batch Size	Related IND or NDA Nos.	Submission Date	Previous Agency Responses on Trial or Protocol with Date of Correspondence
Type 1 Diabetic Subjects						
024/UK	IAsp, 0.15 U/kg	24	07794; 23/11/94 Old production method			
043/DK	IAsp, 0.15 U/kg	18	C96024; 26/9/96 New production method			
Type 2 Diabetic Subjects						
030/DK/N	IAsp, 0.15 U/kg	24	C95001; 16/5/95 Old production method			

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